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Tumours of the Neurohypophysis – One unit's experience and literature review.

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Abstract

- Purpose
  To evaluate and understand the clinical behaviour and radiological correlates of tumours originating from the posterior pituitary gland. To review the management strategy for these rare tumours and add to the limited existing literature.

- Methods
  Retrospective review of eight patients (5 pituicytomas, 2 spindle cell oncocytomas and 1 granular cell tumour) managed at our institution between 2004 and 2019. The patients' clinical course, histological features and radiological findings were reviewed. Their management and long-term follow-up is presented and compared to the literature.

- Results
  Long term follow-up ranged from 1 to 9 years. There was one recurrence in a patient with Spindle Cell Oncocytoma which was treated with radiotherapy. The endoscopically managed cases resulted in complete tumour excision with no recurrence.

- Conclusions
  Epidemiological data on primary tumours of the neurohypophysis is limited due to the rarity of these tumours. This study adds to the literature that these tumours behave as WHO grade I tumours, however, close follow-up is recommended as a few cases have shown recurrence. The endoscopic approach resulted in better gross total tumour resection rate in this series.

Keywords

Pituicytoma
Spindle cell oncocytoma
Granular cell tumour
Neurohypophysis
Sellar region
Transsphenoidal surgery

Pituicytoma and Spindle cell oncocytoma – One unit's experience and literature review.

Introduction

Pituicytoma, spindle cell oncocytoma and granular cell tumour (GCT) of the sellar region are distinct, rare tumours of the neurohypophysis. They are considered as Grade 1 in the 2016 World Health Organization (WHO) classification of tumours of the central nervous system. The International Classification of Diseases for Oncology (ICD-O) codes the behaviour of GCT and spindle cell oncocytoma as 0, meaning they are considered benign tumours. Pituicytoma is coded as 1, meaning unspecified, borderline or uncertain behaviour.(1) These tumours are now considered to have a common origin from pituicytes of the neurohypophysis. This is based on their common immunostaining for the thyroid transcription factor 1 (TTF-1) (2)(3). In the literature to date only 170 cases have been reported, therefore knowledge about their clinical behaviour and growth patterns is limited. Although there is no established optimal therapeutic protocol, full resection is generally agreed to be the treatment goal, in light of emerging reports of recurrence (4). The histological diagnosis is not usually known at the time of surgery however, and since these tumours can be vascular, complete resection is more challenging than for pituitary adenomas and may not always be a safe option (5). Radiological features may hint at an unusual tumour with avid enhancement and flow voids within the tumour having been described (6). We report our unit's experience with these rare tumours over a fifteen-year period and describe the challenges encountered in management as well as review the literature.

Methods

We identified patients from our histopathology database. The clinical manifestations, radiological features and histological characteristics were then reviewed retrospectively. The surgical strategies and long term follow up are also reported. A review of the literature was carried out to identify patterns and similarities reported by other centres.

Results

Between the period of 2004 – 2019, there were eight patients in total, five pituicytomas, two spindle cell oncocytoma and one granular cell tumour, who underwent surgery at our unit. There were five men and three women with a median age at diagnosis of 56. The presentation was varied, four were incidental findings, two patients presented with hypogonadotrophic hypogonadism, one patient presented with visual disturbance and field loss, and one patient presented with an intraventricular haemorrhage into a large tumour. Seven patients underwent transphenoidal resection of the tumour (four microscopic and three endoscopic). One patient who had a large tumour with intraventricular extension underwent a transcranial endoscopic biopsy.

All three endoscopic transphenoidal procedures achieved full clearance of the tumour (case 5, 6 and 7). Out of the four microscopic transphenoidal procedures, one patient had complete resection (Case 1), one had a small residual on the postoperative imaging (Case 3), one resection was subtotal, and this patient had a recurrence of their spindle cell oncocytoma which was discovered on radiological surveillance and was treated with radiotherapy (Case 2). One patient underwent a partial debulking initially. During surgery there was brisk bleeding encountered and the smear initially was reported as meningioma. Afterwards, the formal histopathology revealed a pituicytoma and therefore a further procedure was carried out after three weeks to remove the rest of the tumour (Case 4). One patient who presented with an intraventricular haemorrhage only underwent a biopsy of the tumour (Case 8). (Table 1)

Six out of 8 patients were found to have anterior pituitary dysfunction pre-operatively. Two patients acquired hormone deficiencies post operatively (case 2 and case 3).

The details of each case can be found below categorised according to their surgical management. The case order presented below is based on their sequential presentation to our unit.

Microscopic Transphenoidal resection – Cases 1, 2, 3 and 4

Case 1

55- year old male who presented to the psychosexual clinic with low libido. He was investigated and found to have low testosterone and Growth hormone (GH). Imaging revealed a sellar and suprasellar mass abutting the optic chiasm. He was offered surgery and underwent a microscopic resection. Full clearance was achieved intraoperatively. A CSF leak was noted

during the procedure. A fat graft was applied to the sellar floor and CSF lumbar drainage for five days was instituted. He made a good postoperative recovery but was lost to follow up as he moved to a different region.

Case 2

55-year-old female with Turner's syndrome was found to have a sellar mass, with suprasellar extension, on an MRI scan carried out in 2009 to investigate dizziness. On further investigation she was also found to have low Thyroid stimulating hormone (TSH) and GH as well as a bitemporal field deficit. She underwent a microscopic transsphenoidal resection of what was presumed to be a pituitary adenoma. Histology, however, revealed a moderately cellular tumour composed of spindled cells with plump eosinophilic cytoplasm and elongated variably pleomorphic nuclei. The tumour cells in places were admixed with dense clusters of small reactive lymphocytes. The tumour cells lacked GFAP immunostaining but was TTF1, S100 and EMA positive, in keeping with a spindle cell oncocytoma. The proliferation fraction was low (Figure 1-A).

Surgery was straight forward, however a small residual was seen on the post-operative imaging in the right parasellar region. She developed panhypopituitarism and required cortisol replacement. Annual surveillance imaging was carried out for five years then the interval was increased to two yearly. In 2017, eight years after her surgery, the residual was seen to have increased in size (Figure 2). There was again a suprasellar component which was in close proximity to the optic apparatus. She was offered radiotherapy to this recurrence rather than re-do surgery since she had developed significant cardiac risk factors over the years. She received 54Gy of IMRT over thirty sessions. Further surveillance imaging showed improvement in the tumour bulk. She has now completed 9 years of follow up since her surgery.

Case 3

71-year-old male who sustained a parietal lobe infarct and underwent an MRI which showed an incidental finding of a sellar mass. On surveillance scan the tumour was seen to increase in size and he was offered surgery. He underwent a microscopic transsphenoidal operation in 2010. During surgery the tumour was found to be tough, grey and gelatinous. Histology of the tumour was in keeping with spindle cell oncocytoma comprising cells with elongated nuclei and plump eosinophilic cytoplasm. The tumour cells showed diffuse nuclear labelling for TTF-1, widespread labelling for EMA, patchy immunoreactivity for S100 and absent GFAP

expression. Full clearance was thought to have been achieved during surgery however, a small residual was noted on the postoperative MRI scan. Post operatively the patient was found to have growth hormone deficiency. On surveillance scanning the residual remained stable in size for four years. The patient died from an unrelated cause after five years.

Case 4

80-year-old female found to have a bitemporal hemianopia after complaining of visual disturbance in 2016. She was also found to have a low TSH and cortisol and was started on replacement. Her MRI scan revealed a large sellar and suprasellar mass, elevating and causing compression of the optic chiasm. She underwent a transsphenoidal microscopic resection where the tumour was found to be very vascular. The tumour was debulked but not completely removed due to the brisk bleeding encountered. The tumour cells with elongated nuclei and indistinct cell boundaries were arranged in broad fascicles. (Figure 1- B) The tumour cells were diffusely positive for TTF-1, S-100 and showed weak patchy positivity for Epithelial Membrane Antigen (EMA), which in conjunction with the morphology confirmed pituicytoma, WHO grade I.

Given this histological diagnosis, she underwent a further operation a few weeks later to further debulk the tumour due to the increased likelihood of recurrence. She has now completed three years of follow up with no signs of tumour recurrence. (Figure 3)

Endoscopic Resection – Cases 5, 6 and 7

Case 5

56-year-old male presented with a one-year history of loss of body hair, low libido and low muscle mass. He was found to have hypogonadotrophic hypogonadism as well as low cortisol, secondary hypothyroidism and a raised prolactin. His MRI scan revealed a sellar and suprasellar mass distorting the pituitary stalk but not in contact with his optic chiasm (Figure 4, A and B). He underwent endoscopic transsphenoidal resection in 2015 where a gross total resection was achieved radiologically. The tumour was firm and rubbery and moderate bleeding was encountered during surgery. The histology and immunoprofile (notably nuclear labelling for TTF-1 in the tumour cells) was compatible with a pituicytoma, WHO grade I. He is currently undergoing annual surveillance imaging where no tumour recurrence has been noted.

Case 6

44-year-old male with an incidental finding of a sellar mass on an MRI scan done to investigate headaches. Further investigation revealed primary hypothyroidism. The MRI revealed an avidly enhancing sellar and suprasellar mass (Figure 4, C and D). The radiological differential diagnosis included histiocytosis, germ cell tumour, craniopharyngioma, pituicytoma and astrocytoma. He underwent an extended endoscopic resection of his mass were a complete resection was achieved. He made a good recovery and has completed two years of follow up. Histology showed a moderately cellular lesion with the majority of cells demonstrating spindle shaped morphology. Immunohistochemistry showed the tumour cells to be positive for TTF-1 (nuclear) as well as S100.

Case 7

36-year-old female with an incidental finding of a sellar mass on a CT scan that was carried out to investigate a transient episode of weakness. On further investigation, it transpired that this mass had already been discovered 9 years prior at another hospital, also incidentally. At the time the patient was told that this was an incidental finding of a non-functioning pituitary adenoma and she was discharged.

An MRI scan revealed that this mass had increased in size over the nine-year period and it was now abutting the optic chiasm. Visual field testing revealed a superior quadrantanopia (Figure 5).

Given the significant change in size and the threat to her vision, surgery was offered.

The lesion was completely resected via an endoscopic transsphenoidal approach. Histology revealed a cellular tumour composed of sheets of plump and spindled granular cells with abundant eosinophilic cytoplasm. There were minimal atypia and mitotic activity with no necrosis. Immunohistochemistry showed delicate membranous GFAP staining. EMA was negative and S-100 showed patchy expression in granule cells. TTF-1 was positive in tumour cells with a low Ki-67. Based on the morphological features, the diagnosis of granular cell tumour rather than pituicytoma or spindle cell oncocytoma was made.

Case 8

56-year-old gentleman who presented with headache and confusion in 2018, was found on CT scan to have an intraventricular haemorrhage with an underlying mass and ventriculomegaly. The MRI revealed a suprasellar mass extending into the ventricle (Figure 6). He underwent a

transcranial endoscopic septostomy and biopsy of the tumour and insertion of a ventriculo-peritoneal shunt. Histology revealed a moderately cellular tumour with spindled morphology and immunoreactivity for TTF-1 and focally S-100, in keeping with pituicytoma, WHO grade I. The patient was managed conservatively since his performance status was poor. Invasive treatment was not deemed appropriate by the multi-disciplinary team.

Discussion

Pituicytoma, spindle cell oncocytoma and GCTs are rare entities (1). Even in our large Neurosurgical centre, with over two hundred pituitary surgeries performed per year, only eight patients were diagnosed over a fifteen-year period. In the literature there are less than 300 reported cases to date, consisting mostly of case reports and a few case series of 2 – 11 patients.(Table 2) (1,3,7–12)(2,4,7–13) Both pituicytoma and spindle cell oncocytoma were recognised as new and separate brain tumour entities and first included in the fourth edition of the WHO Classification of Tumours of the Nervous System (WHO 2007) (14-15). Since then increasing evidence suggests that pituicytoma and spindle cell oncocytoma, in addition to granular cell tumour of the sellar region, may constitute a spectrum of a single biological tumour entity (1). Since the first description of these tumours, it has been demonstrated that all three entities, similar to normal, non-neoplastic pituicytes, show diffuse immunoreactivity for TTF-1. Therefore it is plausible that granular cell tumours of the sellar region and spindle cell oncocytomas are variants of pituicytoma with either lysosome-rich or mitochondria-rich cytoplasm (2). Based on this, it has also been proposed to reclassify spindle cell oncocytomas as oncocytic pituicytomas and granular cell tumours as granular cell pituicytomas. The clinical presentation is from mass effect of the tumour, thus similar to non-functioning pituitary adenomas and the diagnosis is therefore rarely suspected preoperatively. In our series, the diagnosis was suspected in only one case preoperatively (case 6) and this was based on imaging. Endocrine dysfunction was highly prevalent in our series with 6 out of the 8 patients found to have pre-operative deficiency in at least one pituitary hormonal axis. Case 8 presented with intraventricular haemorrhage and therefore his endocrine status prior to surgery was unknown.

The radiographic features on MRI are similar to pituitary adenomas with the tumour being isointense on T1. However, unlike an adenoma, these tumours tend to have a missing posterior pituitary bright spot. This is likely to be due to the fact that these tumours arise from the

neurohypophysis or the infundibulum and therefore the normal posterior pituitary gland cannot be seen separate to the tumour, however this also depends on the growth pattern of the tumour. They also tend to show avid and homogenous enhancement with gadolinium. (16,17) In our series the degree of enhancement varied considerably and was not always avid (Figure. 4 A and B). Flow voids could be seen in some of the cases (Figure. 4 C and Figure 6 C).

In our series, all tumours were found to be firmer and more vascular than a typical adenoma, making the operation more challenging and total tumour resection more difficult to achieve. Bleeding is a common complication in these types of tumours, both intra-operatively and post-operatively. One patient was reported to have died in the early post-operative period from haemorrhage. (18) Intra-operative haemorrhage often leads to subtotal resection as happened with case 4 in our series. Second stage procedure may be required to attempt full resection.(19) Some authors have reported pre-operative embolization prior to proceeding with re-operation for any residual or recurrent tumour. (20)

Out of the reported cases of surgical complications, 50 cases report haemorrhage as a post-op complication. (13) We found one other reported case of a spindle cell oncocytoma which presented with apoplexy and intraventricular haemorrhage.(21) One case was reported as presenting with intermittent epistaxis from a nasopharyngeal mass.(22)

When there is any suspicion that this might be the underlying diagnosis the surgeon should be aware that this may be very vascular and be prepared for this. Such tumours may be impossible to remove fully and also present an added risk of post-operative haemorrhage.

The endoscopic approach was more successful in our experience and both patients who had their tumour removed endoscopically had complete resection. On the other hand, from the three patients who had a microscopic resection, one experienced a recurrence, one was a partial resection and one was a complete but staged resection. All the tumours had a degree of suprasellar extension, and we find that the endoscope is more suited to achieve resection of such a component. However, the number of cases in our series is too small to support a difference in outcomes between the microscopic and endoscopic approach. Case 6 was suspected to have a non-adenomatous neoplasm and thus underwent an extended endoscopic approach, using long, zero and 30-degree endoscopes. The cavitron ultrasonic surgical aspirator (CUSA) was used in the endoscopic cases to debulk the tumour.

Histology of all tumours revealed a moderately cellular neoplasm comprising fascicles of spindle-shaped cells. None of the tumours showed any obvious cytological atypia or brisk mitotic activity. The single GCT case (Case 7) showed granular cells on microscopy but with a similar immunohistochemistry profile to the other cases. All tumours also had low Ki-67 proliferation index of around 3-5%.
All tumours showed diffuse nuclear labelling for TTF-1 and variable labelling for EMA, S100 and GFAP. These findings were similar to other reported case series of pituicytomas.(12)

The clinical implications of a diagnosis of pituicytoma, spindle cell oncocytoma or GCT, are based on case reports and small case series. Long term follow-up is recommended by most authors due to the chance of recurrence especially due to the difficulty in achieving gross total resection.(11)(22) However, whether the chance of recurrence is higher than that of pituitary adenomas is not possible to tell. In our series there was one recurrence in a patient who was known to have a small residual postoperatively. The growth was noticed eight years after the surgical resection. Radiotherapy appears to have controlled this growth and a reduction in tumour size has been noticed. Other cases of successful radiotherapy to treat a recurrence have been reported. (4) Patients should be informed about the risk of recurrence and a conversation regarding radiotherapy to any tumour residual should be had.

Conclusion

Pituicytomas, spindle cell oncocytomas and GCTs are diagnosed histologically and imaging alone is not able to distinguish them from pituitary adenomas. Positive nuclear labelling for TTF-1 is a requirement for diagnosis. These are rare tumours and often operatively challenging. If at surgery, an unusually vascular and tough tumour is encountered, these tumours should be kept in mind. The aim should be complete resection, and, in our experience, this is more likely to be achieved endoscopically. Life-long follow-up is recommended as there is a higher chance of recurrence than with pituitary adenomas. Radiotherapy can be successful to treat recurrence.

Figure captions:

Fig.1 Histology of spindle cell oncocytoma and pituicytoma
On haematoxylin and eosin (H&E) stained sections the tumour cells in spindle cell oncocytoma (A, Case 2) are composed of cells with elongated nuclei and conspicuous eosinophilic cytoplasm, whilst in pituicytoma (B, Case 4), the tumour cells have elongated nuclei and indistinct cell boundaries. In both tumours there is diffuse nuclear immunoreactivity for TTF1 (A1 and B1), and the Ki67 proliferation fraction assessed with MIB1 antibody is low (A2 and B2).
Scale bar is 100μm in A, B, A2 and B2 and 200 μm in A1 and B1.

Fig. 2 Case 2 A) Preoperative MRI coronal FLAIR image through sella. B) five years post-operative scan coronal T1 with gadolinium. C) eight years post-op scan showing increase in size of the residual tumour.

Fig. 3 Case 4 A) Preoperative coronal T1 MRI scan showing sellar and suprasellar tumour. B) MRI scan obtained after the first operation, prior to further tumour debulking a few weeks later. C) Most recent follow-up scan showing no residual tumour.

Fig. 4 – Case 5 (A and B) and Case 6 (C and D). There was variability in the degree of contrast enhancement. A) Case 5, Sagittal T1 MRI without gadolinium and B) with gadolinium. C) Case 6, axial T1 with gadolinium and D) sagittal T1 without contrast.

Fig. 5 – Case 7 A) Preoperative sagittal T1 MRI showing a suprasellar lesion distinct from the pituitary gland. B) Axial T2 MRI, C) Coronal enhanced T1 MRI and D) Coronal T2 MRI showing the tumour to be in contact with the optic chiasm causing a mild superior visual field defect on the left. E) Humphrey visual field test.

Fig. 6 – Case 8 - A) Sagittal MRI T1 sequence showing a suprasellar tumour extending into the third ventricle. B) Coronal T1 MRI with gadolinium showing avid enhancement. C) Axial T2 showing a solid tumour with flow voids representing blood vessels.

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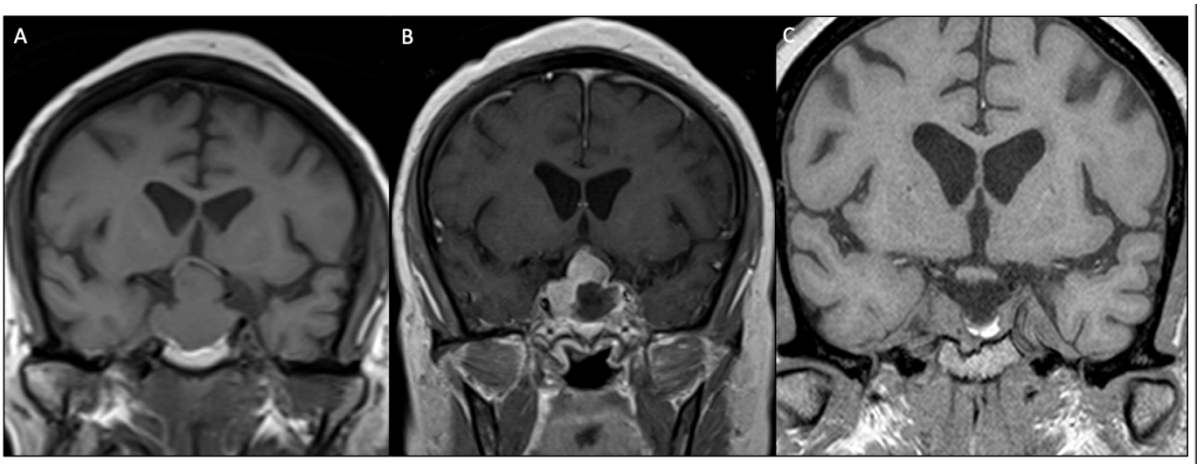
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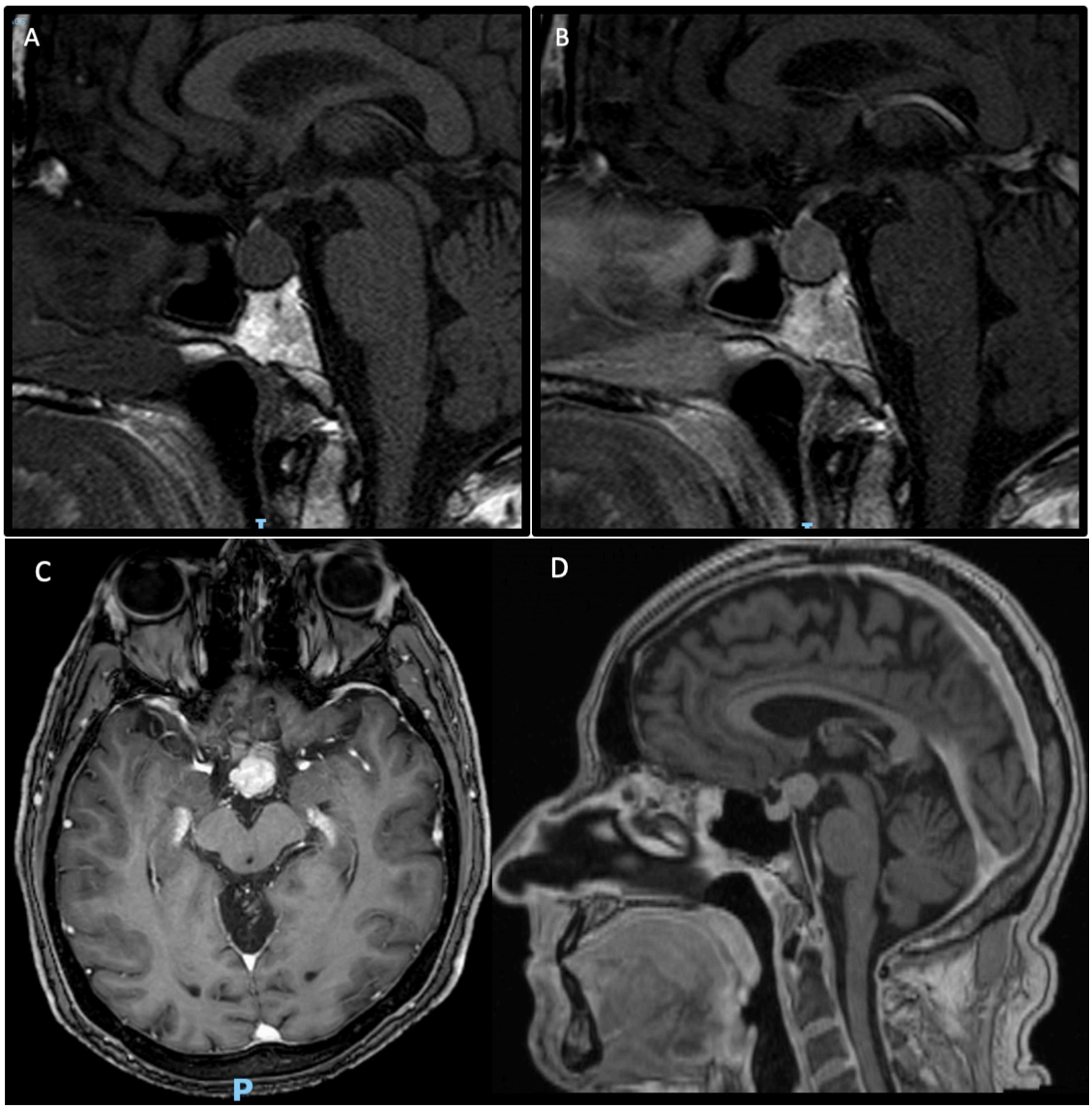
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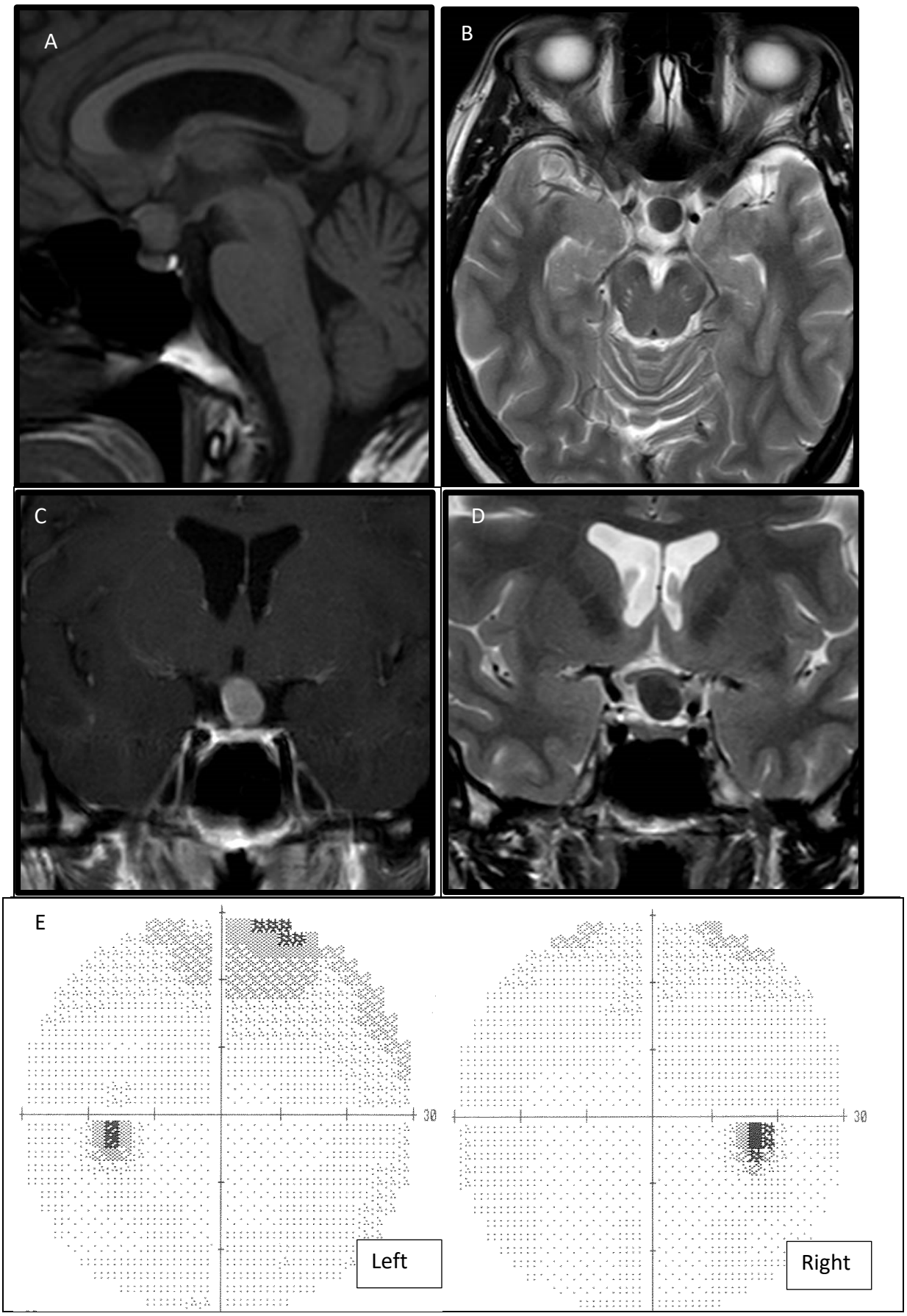
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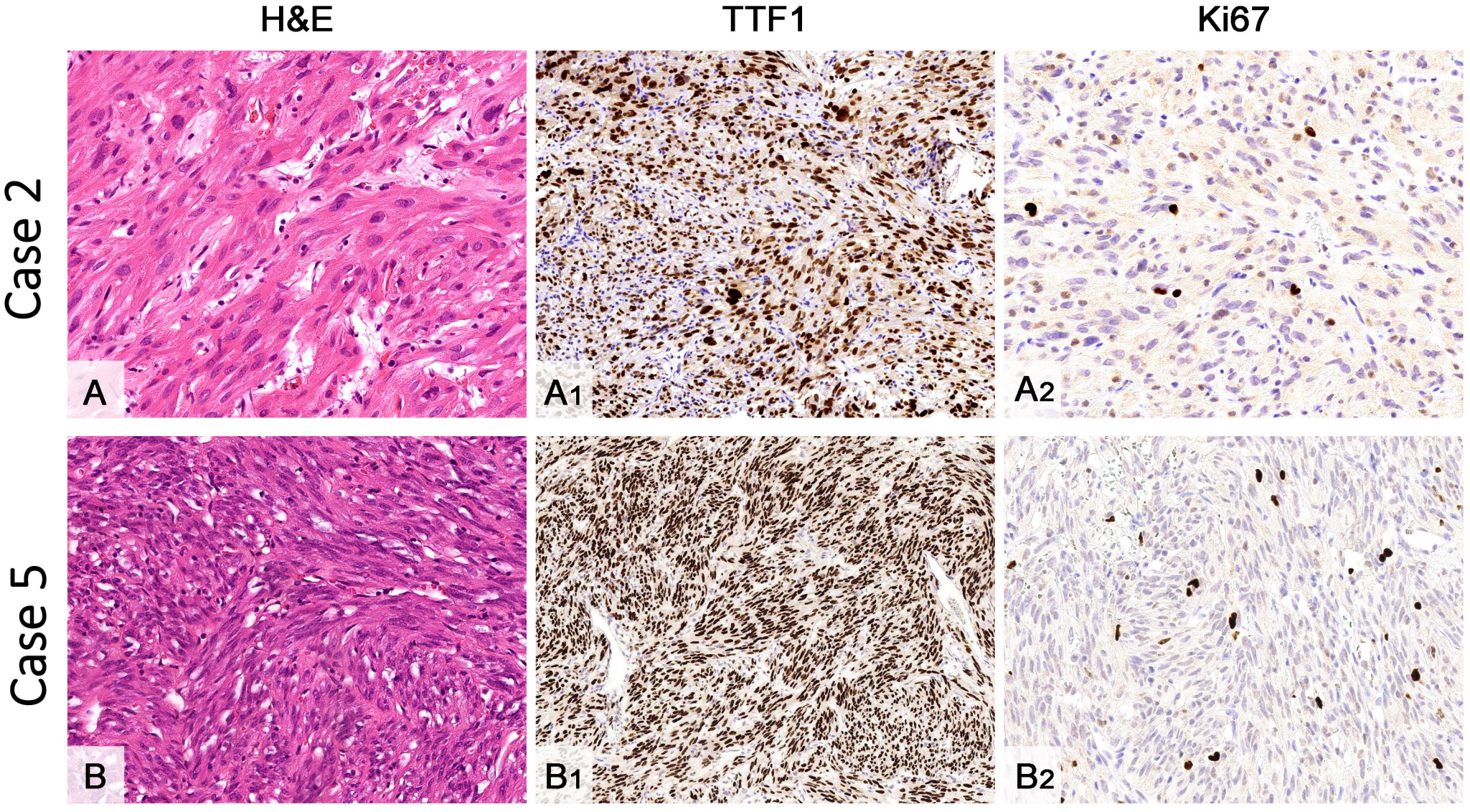
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Tumour Type	Number of Cases	Largest Case series	Received Radiotherapy	Residual	Recurrence
Pituicytoma	135 49 single case reports, 21 short case series (1-54)	11	10	41	6
Spindle cell Oncocytoma	50 21 single case reports, 10 Short case series (1,3,8,9) (55-80)	5	9	28	1
Granular cell tumour	69 27 single case reports, 11 short case series (1,7,9,81-112)	10	6	19	5

Table 2 – Summary of case reports and case series in the literature reporting the management and outcomes of Pituicytomas, Spindle cell Oncocytomas and Granular cell tumours.

Table 1

Case	Histological diagnosis	Age Gender	Presentation Year	Surgery	Full clearance	Recurrence	Follow up
1	**Pituicytoma**	55 M	Hypogonadotrophic hypogonadism 2004	Microscopic	Yes	N/A	N/A
2	**Spindle cell Oncocytoma**	55 F	Incidental 2009	Microscopic	No	Yes	9 years
3	**Spindle cell Oncocytoma**	71 M	Incidental 2010	Microscopic	Yes	No	4 years
4	**Pituicytoma**	80 F	Visual disturbance (bitemporal hemianopia) 2016	Microscopic (Re-do 3 weeks later)	No	No	3 years
5	**Pituicytoma**	56 M	Hypogonadotrophic hypogonadism 2015	Endoscopic	Yes	No	4 years
6	**Pituicytoma**	44 M	Incidental 2016	Endoscopic	Yes	No	2 years
7	**Granular cell tumour**	36 F	Incidental 2019	Endoscopic	Yes	No	6 months
8	**Pituicytoma**	56 M	Intraventricular haemorrhage 2018	Endoscopic biopsy	N/A	No	N/A

Summary of eight tumours of the neurohypohysis (5 Pituicytoma, 2 Spindle cell oncocytoma and 1 GCT) managed at a single Neurosurgical centre.